

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Protocol Comparing Aspirin versus Low-Molecular-Weight Heparin for Blood Clot Prevention in Orthopaedic Trauma Patients
AUTHORS	O'Toole, Robert; Stein, DM; Frey, Katherine; O'Hara, Nathan; Scharfstein, Daniel; Slobogean, Gerard; Joseph, Tara; Haac, Bryce; Carlini, Anthony; Manson, Theodore; Sudini, Kuladeep; Mullins, C; Wegener, Stephen; Firoozabadi, Reza; Haut, Elliott; Bosse, Michael; Seymour, Rachel; Holden, Martha; Gitajn, Ida; Goldhaber, Samuel; Eastman, Alexander; Jurkovich, Gregory; Vallier, Heather; Gary, Joshua; Kleweno, Conor; Cuschieri, Joseph; Marvel, Debra; Castillo, Renan

VERSION 1 – REVIEW

REVIEWER	Suzanne Cannegieter Leiden University Medical Center Leiden the Netherlands
REVIEW RETURNED	20-Jul-2020

GENERAL COMMENTS	<p>This manuscript describes the protocol of a randomised controlled trial designed to determine if aspirin is non-inferior to LMWH in preventing death due to PE in fracture patients.</p> <p>The topic concerns an important clinical question that applies to a large number of patients. The study design is described in great detail and every aspect is well thought through, including strong patient and other stakeholders involvement. In fact, the protocol is very good, leaving just a few major issues:</p> <p>1) can the others explain why they chose for aspirin as oral medication and did not consider DOACs? Some rationale on this choice would be welcome.</p> <p>2) Although the Outcome Ascertainment and Adjudication seems well organised, the establishment of the primary study outcome is a weak point of the study. Even with this organisation in place, misclassification of the outcome will occur, as death due to PE is not straightforward to establish as the authors also recognise. Especially in a non-inferiority design this is an issue, as it will dilute a true difference and bring the incidence measures closer together, which may lead to falsely concluding on non-inferiority whereas in fact one treatment can be superior/inferior. Why not include all VTE as a primary outcome to solve this?</p> <p>Minor comment: the study is rather US oriented, can the authors adapt the text somewhat to make it more internationally applicable?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

This manuscript describes the protocol of a randomised controlled trial designed to determine if aspirin is non-inferior to LMWH in preventing death due to PE in fracture patients.

The topic concerns an important clinical question that applies to a large number of patients. The study design is described in great detail and every aspect is well thought through, including strong patient and other stakeholders involvement. In fact, the protocol is very good, leaving just a few major issues:

1) can the others explain why they chose for aspirin as oral medication and did not consider DOACs? Some rationale on this choice would be welcome.

Response: We decided to use aspirin as the study intervention instead of other DOACs for several reasons. While the evidence for aspirin to prevent VTE in orthopaedic trauma patients is limited, there is substantial evidence for the use of aspirin for VTE prophylaxis in arthroplasty patients (Hood 2019, Rondon 2019). Given the similarities in the patient population and overlap in healthcare providers that treat fracture patients and arthroplasty patients, aspirin is commonly used for chemoprophylaxis in fracture patients (Sagi 2015).

We acknowledge an emerging body of evidence suggests DOACs may be at least as effective as aspirin for preventing venous thromboembolism in arthroplasty patients (Matharu 2020, Anderson 2018). Many of these studies were not available at the time of designing our trial. Further, this research has also not been extended to orthopaedic trauma patients. Concerns regarding an increased risk of bleeding for DOACs compared to aspirin remain (Bala 2017, Nielsen 2017).

In our pre-trial patient preference research, the cost of VTE prevention was of considerable importance to patients (Haac 2017). Aspirin is substantially less expensive than DOACs and more widely available.

Finally, our pilot trial results suggest aspirin and low-molecular weight heparin may be similar in their protective effects against thrombotic events in fracture patients (Haac 2020).

Revision: We acknowledge an emerging body of evidence that suggests direct oral anticoagulants may be comparable to aspirin in preventing VTE in arthroplasty patients.^{21,22} However, there remain concerns regarding an increased risk of bleeding for direct oral anticoagulants compared to aspirin.^{23,24} Direct oral anticoagulants are also more costly than aspirin, making them less favorable from a patient perspective.²⁵ [Introduction]

References:

Hood BR, Cowen ME, Zheng HT, Hughes RE, Singal B, Hallstrom BR. Association of Aspirin With Prevention of Venous Thromboembolism in Patients After Total Knee Arthroplasty Compared With Other Anticoagulants: A Noninferiority Analysis. *JAMA Surg*. 2019 Jan 1;154(1):65-72.

Rondon AJ, Shohat N, Tan TL, Goswami K, Huang RC, Parvizi J. The Use of Aspirin for Prophylaxis Against Venous Thromboembolism Decreases Mortality Following Primary Total Joint Arthroplasty. *J Bone Joint Surg Am*. 2019 Mar 20;101(6):504-513.

Sagi HC, Ahn J, Ciesla D, Collinge C, Molina C, Obrebsky WT, Guillaumondegui O, Tornetta P 3rd; Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee. Venous Thromboembolism Prophylaxis in Orthopaedic Trauma Patients: A Survey of OTA Member Practice Patterns and OTA Expert Panel Recommendations. *J Orthop Trauma*. 2015 Oct;29(10):e355-62.

Matharu GS, Garriga C, Whitehouse MR, Rangan A, Judge A. Is Aspirin as Effective as the Newer Direct Oral Anticoagulants for Venous Thromboembolism Prophylaxis After Total Hip and Knee Arthroplasty? *An*

Analysis From the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man. *J Arthroplasty*. 2020 Sep;35(9):2631-2639.e6.

Anderson DR, Dunbar M, Murnaghan J, Kahn SR, Gross P, Forsythe M, Pelet S, Fisher W, Belzile E, Dolan S, Crowther M, Bohm E, MacDonald SJ, Gofton W, Kim P, Zukor D, Pleasance S, Andreou P, Doucette S, Theriault C, Abianui A, Carrier M, Kovacs MJ, Rodger MA, Coyle D, Wells PS, Vendittoli PA. Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. *N Engl J Med*. 2018 Feb 22;378(8):699-707.

Bala A, Huddleston JI 3rd, Goodman SB, Maloney WJ, Amanatullah DF. Venous Thromboembolism Prophylaxis After TKA: Aspirin, Warfarin, Enoxaparin, or Factor Xa Inhibitors? *Clin Orthop Relat Res*. 2017 Sep;475(9):2205-2213.

Nielen JT, Dagnelie PC, Emans PJ, Veldhorst-Janssen N, Lalmohamed A, van Staa TP, Boonen AE, van den Bemt BJ, de Vries F. Safety and efficacy of new oral anticoagulants and low-molecular-weight heparins compared with aspirin in patients undergoing total knee and hip replacements. *Pharmacoepidemiol Drug Saf*. 2016 Nov;25(11):1245-1252.

Haac BE, O'Hara NN, Mullins CD, Stein DM, Manson TT, Johal H, Castillo R, O'Toole RV, Slobogean GP. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. *BMJ Open*. 2017 Aug 11;7(8):e016676.

Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, Stein DM; ADAPT Investigators. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial. *PLoS One*. 2020 Aug 3;15(8):e0235628.

2) Although the Outcome Ascertainment and Adjudication seems well organised, the establishment of the primary study outcome is a weak point of the study. Even with this organisation in place, misclassification of the outcome will occur, as death due to PE is not straightforward to establish as the authors also recognise. Especially in a non-inferiority design this is an issue, as it will dilute a true difference and bring the incidence measures closer together, which may lead to falsely concluding on non-inferiority whereas in fact one treatment can be superior/inferior. Why not include all VTE as a primary outcome to solve this?

Response: We thank the reviewer for raising the concern of the misclassification of PE-related death biasing the trial towards non-inferiority. The comment motivated the trial's steering committee to change the primary endpoint from PE-related death to all-cause mortality. Cause-specific mortality will remain as a secondary efficacy outcome, along with VTE events (PE and DVT).

As you mention, misclassification of the primary outcome of PE-related death would bias the results to non-inferiority and be a major threat to the internal validity of the trial. After several meetings, we confirmed that all-cause mortality was viewed as more important than PE-related death by our patient stakeholder and protocol committees and had greater scientific reliability. The change in the primary outcome increased the anticipated base rate from 0.25% to 1.00%. The increased non-inferiority margin from 0.36% to 0.75% was found acceptable through a survey of patients and clinical experts. With this change we maintain over 95% power with our 12,200 target sample size to declare non-inferiority based on the upper bound of a two-sided 96.2% confidence interval, which account for the two interim analyses. The DSMB was not involved in these decisions due to their knowledge of treatment effect from masked interim analyses. The decision of the trial's steering committee to change the primary outcome and non-inferiority margin was supported by the protocol committee, patient stakeholder committee, and sponsor. Our process for changing the primary outcome adherence to the suggestions published by Evans (2007) and Wittes (2002).

Revisions:

The primary outcome is all-cause mortality. We will evaluate non-inferiority by testing whether the

intention-to-treat difference in the probability of dying within 90 days of randomization between aspirin and LMWH is less than our non-inferiority margin of 0.75%. [Abstract, Methods and Analysis]

The primary aim of PREVENT CLOT is to compare aspirin to LMWH for thromboprophylaxis in orthopaedic trauma patients. We hypothesize that aspirin is non-inferior to LMWH in preventing all-cause mortality within 90-days of randomization. The secondary objective is to compare the effects of aspirin versus LMWH in preventing cause-specific mortality, non-fatal PE, deep vein thrombosis (DVT), bleeding complications, wound complications, and deep surgical site infections within 90-days of randomization. [Introduction]

The primary study outcome is all-cause mortality within 90 days of randomization.

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The primary outcome was changed from PE-related death to all-cause mortality during the course of the trial. At the recommendation of an external peer reviewer for the protocol manuscript, the trial's steering committee determined that it was unfeasible to adjudicate death due to pulmonary embolism (PE) with reasonable certainty. Misclassification of the primary outcome of PE-related death would bias the results to non-inferiority. As such, the trial's steering committee decided to change the primary outcome from PE-related death to all-cause mortality. All-cause mortality was viewed as more important than PE-related death by our patient stakeholder and protocol committees and had greater scientific reliability. The DSMB was not involved in these decisions due to their knowledge of treatment effect from interim analyses. The decision of the trial's steering committee to change the primary outcome and non-inferiority margin was supported by the protocol committee, patient stakeholder committee, and sponsor.

[Methods and Analysis]

The primary hypothesis is that aspirin will be non-inferior to LMWH with respect to all-cause mortality. The trial's non-inferiority margin was derived from patient preference research and a survey of clinical experts that indicated a willingness to accept a 0.75% absolute increase in the risk of death in exchange for a specific set of benefits related to aspirin over LMWH.²⁵ [Methods and Analysis]

To evaluate the primary hypothesis regarding all-cause mortality, we will compare the upper bound of a two-sided 96.2% confidence interval for the primary intention to treat estimand to the pre-specified non-inferiority margin of 0.75%. [Methods and Analysis]

References:

Evans S. When and how can endpoints be changed after initiation of a randomized clinical trial? PLoS Clin Trials. 2007 Apr 13;2(4):e18.

Wittes J. On changing a long-term clinical trial midstream. Stat Med. 2002 Oct 15;21(19):2789-95. doi: 10.1002/sim.1282. PMID: 12325094.

Minor comment:

the study is rather US oriented, can the authors adapt the text somewhat to make it more internationally applicable?

Response: The study is funded by the Patient-Centered Outcomes Research Institute. The Institute was created as part of the Affordable Care Act (ObamaCare) and is mandated by the United States government to focus on United States-specific research. As such, we focus much of our justification for the trial to the United States.

However, your point is well-taken. The findings of the trial will be of interest internationally and we have made several revisions to incorporate the international relevance of the trial.

Revisions: Globally, over 130 million people sustain a fracture each year.² [Introduction]

As such, many Level-1 trauma centers in the United States and elsewhere routinely use LMWH for fracture patients if they are not contraindicated for chemoprophylaxis. [Introduction]

The results of these studies have led the European Society of Anaesthesiologists to recommend aspirin for VTE prophylaxis in arthroplasty and hip fracture patients.⁷ [Introduction]

VERSION 2 – REVIEW

REVIEWER	Suzanne Cannegieter Leiden University Medical Center, Leiden, the Netherlands
REVIEW RETURNED	23-Feb-2021
GENERAL COMMENTS	This protocol of a randomised controlled trial designed to determine if aspirin is non-inferior to LMWH in preventing death in fracture patients has been carefully revised according to my earlier questions. I much appreciate the work that has gone into this and have no further comments, and look forward to the results.